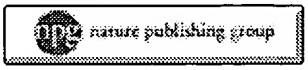
1: Oncogene. 1999 Apr 1; 18(13): 2241-51. Related Articles, Links



Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers.

Pegram M, Hsu S, Lewis G, Pietras R, Beryt M, Sliwkowski M, Coombs D, Baly D, Kabbinavar F, Slamon D.

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Previous studies have demonstrated a synergistic interaction between rhuMAb HER2 and the cytotoxic drug cisplatin in human breast and ovarian cancer cells. To define the nature of the interaction between rhuMAb HER2 and other classes of cytotoxic drugs, we applied multiple drug effect/combination index (CI) isobologram analysis to a variety of chemotherapeutic drug/rhuMAb HER2 combinations in vitro. Synergistic interactions at clinically relevant drug concentrations were observed for rhuMAb HER2 in combination with cisplatin (CI=0.48, P=0.003), thiotepa (CI=0.67, P=0.0008), and etoposide (CI=0.54, P=0.0003). Additive cytotoxic effects were observed with rhuMAb HER2 plus doxorubicin (CI=1.16, P=0.13), paclitaxel (CI=0.91, P=0.21), methotrexate (CI=1.15, P=0.28), and vinblastine (CI=1.09, P=0.26). One drug, 5-fluorouracil, was found to be antagonistic with rhuMAb HER2 in vitro (CI=2.87, P=0.0001). In vivo drug/rhuMAb HER2 studies were conducted with HER-2/neu-transfected, MCF7 human breast cancer xenografts in athymic mice. Combinations of rhuMAb HER2 plus cyclophosphamide, doxorubicin, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant reduction in xenograft volume compared to chemotherapy alone (P<0.05). Xenografts treated with rhuMAb HER2 plus 5-fluorouracil were not significantly different from 5-fluorouracil alone controls consistent with the subadditive effects observed with this combination in vitro. The synergistic interaction of rhuMAb HER2 with alkylating agents, platinum analogs and topoisomerase II inhibitors, as well as the additive interaction with taxanes, anthracyclines and some antimetabolites in HER-2/neu-overexpressing breast cancer cells demonstrates that these are

rational combinations to test in human clinical trials.

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Concept Details

Paclitaxel

A cyclodecane isolated from the bark of the Pacific yew tree, TAXUS BREVIFOLIA. It stabilizes MICROTUBULES in their polymerized form leading to cell death.

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                - Taxoids
              - **Paclitaxel**